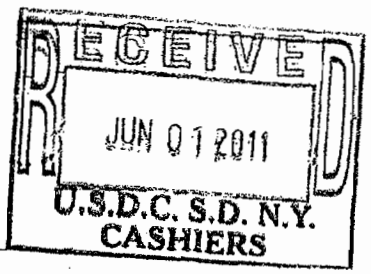
11 CV 3721

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK

PFIZER INC., PFIZER LIMITED, and PFIZER IRELAND PHARMACEUTICALS, Plaintiffs, v. WATSON PHARMACEUTICALS, INC. and WATSON LABORATORIES, INC. Defendants.	Civil Action No.



COMPLAINT FOR PATENT INFRINGEMENT

Pfizer Inc., Pfizer Limited, and Pfizer Ireland Pharmaceuticals (collectively "Pfizer" or "Plaintiffs"), by their attorneys, for their complaint against Watson Pharmaceuticals, Inc. and Watson Laboratories, Inc. (collectively "Watson" or "Defendants"), allege as follows:

NATURE OF THE ACTION

1. This is an action by Pfizer against Defendants for patent infringement of United States Patent No. 6,469,012 (the "'012 patent"). This action arises out of Defendants' filing of an Abbreviated New Drug Application ("ANDA") seeking approval by the United States Food and Drug Administration ("FDA") to sell generic copies of Pfizer's revolutionary oral treatment for erectile dysfunction, Viagra®, prior to the expiration of the '012 patent owned by Pfizer.

THE PARTIES

2. Pfizer Inc. is a corporation organized under the laws of the State of Delaware and has its principal place of business located at 235 East 42nd Street, New York, New York. Pfizer invests extensively in designing, developing, and evaluating new and innovative pharmaceutical products and sells pharmaceutical products to the public throughout the United States.

3. Pfizer Limited is a corporation organized under the laws of England and has its principal place of business at Ramsgate Road, Sandwich, Kent, England

4. Pfizer Ireland Pharmaceuticals is a private unlimited liability company incorporated in Ireland having its registered office at Operations Support Group, Ringaskiddy, Co Cork, Ireland.

5. Pfizer has all right, title, and interest in the '012 patent and the right to sue for infringement thereof.

6. On information and belief, defendant Watson Pharmaceuticals, Inc. ("Watson Pharmaceuticals") is a corporation organized and existing under the laws of Nevada, having its principal place of business at Morris Corporate Center III, 400 Interpace Parkway, Parsippany, New Jersey 07054.

7. On information and belief, defendant Watson Laboratories, Inc. ("Watson Laboratories") is a corporation organized and existing under the laws of Nevada, having its principal place of business at 311 Bonnie Circle, Corona, California 92880.

8. On information and belief, Watson Laboratories is a wholly owned subsidiary of Watson Pharmaceuticals.

JURISDICTION AND VENUE

9. This action arises under the patent laws of the United States, Title 35, United States Code. The Court has subject matter jurisdiction over this action pursuant to the provisions of 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

10. Venue is proper in this judicial district pursuant to the provisions of 28 U.S.C. §§ 1391 and 1400(b).

11. Watson Pharmaceuticals is subject to personal jurisdiction in New York under CPLR 301 and 302(a) due, among other things, to Watson Pharmaceuticals' systematic,

purposeful, and continuous contacts in this district. On information and belief, Watson Pharmaceuticals has purposefully availed itself of this forum by making, shipping, using, offering to sell or selling, or causing others to use, offer to sell, or sell, pharmaceutical products in the State of New York including in this district and deriving revenue from such activities. Upon information and belief, Watson Pharmaceuticals owns properties and conducts business at the following locations in New York: Carmel, New York; Copiague, New York; and Brewster, New York.

12. Watson Laboratories is subject to personal jurisdiction in New York under CPLR 301 and 302(a) due, among other things, to Watson Laboratories' systematic, purposeful, and continuous contacts in this district. On information and belief, Watson Laboratories has purposefully availed itself of this forum by making, shipping, using, offering to sell or selling, or causing others to use, offer to sell, or sell, pharmaceutical products in the State of New York including in this district and deriving revenue from such activities. On information and belief, Watson Laboratories is registered to do business in New York.

BACKGROUND

The '012 Patent

13. On October 22, 2002, the United States Patent and Trademark Office ("USPTO") issued the '012 patent, titled "Pyrazolopyrimidinones for the Treatment of Impotence," based on an application filed by Dr. Peter Ellis and Dr. Nicholas Kenneth Terrett. Drs. Ellis and Terrett duly and legally assigned the '012 patent to Pfizer Inc. The USPTO, during the course of reexamination proceedings, has confirmed the patentability of claims 1–23, 25, and 26 of the '012 patent over numerous prior art references. The USPTO found claim 24 not patentable. Pfizer is only asserting claims 25 and 26 of the '012 patent in this case. A copy of the '012 patent is attached hereto as Exhibit A.

14. Pfizer Limited is the owner of a beneficial interest in the '012 patent.

15. Pfizer Ireland Pharmaceuticals is an exclusive licensee under the '012 patent.

Orange Book Listing for Viagra®

16. Pfizer holds an approved New Drug Application for treating erectile dysfunction with sildenafil citrate which Pfizer sells under the registered name Viagra®. Treatment of erectile dysfunction with Viagra® is covered by the '012 patent. Pursuant to 21 U.S.C. § 355(b)(1) and the regulations the FDA has promulgated pursuant thereto, the '012 patent is listed in the FDA publication titled "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book") for treatment of erectile dysfunction.

17. The Orange Book lists the '012 patent's expiration date as October 22, 2019.

18. The Orange Book also lists United States Patent No. 5,250,534 (the "'534 patent") with respect to Viagra®, and lists the '534 patent's expiration date as March 27, 2012.

Watson's ANDA

19. By letter dated May 3, 2011 (the "Watson Notice Letter"), Watson Laboratories notified Pfizer Inc. that it had filed ANDA No. 202506 with the FDA, seeking approval under the Federal Food, Drug and Cosmetic Act ("FDCA") to market and sell, prior to the expiration of the '012 patent, 25 mg, 50 mg, and 100 mg tablets of sildenafil citrate, generic copies of Viagra®, for treatment of erectile dysfunction (the "ANDA Products").

20. The Watson Notice Letter states that ANDA No. 202506 contains a "Paragraph IV" certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV), alleging that "the '012 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, or sale" of Watson's ANDA Products prior to the date of the expiration of the '012 patent.

21. On information and belief, Watson Pharmaceuticals and Watson Laboratories collaborated and acted in concert in the decision to file and the filing of ANDA No. 202506.

COUNT I
(Patent Infringement by Defendant Watson)

22. The allegations of paragraphs 1-21 above are repeated and re-alleged as if set forth fully herein.

23. Pursuant to 35 U.S.C. § 271(e)(2)(A), Watson's filing of ANDA No. 202506 seeking approval to market Watson's ANDA Products is an act of infringement of each of claims 25 and 26 of the '012 patent entitling Pfizer to the relief provided by 35 U.S.C. § 271(e)(4), including, *inter alia*, an order of this Court that the effective date of approval for ANDA No. 202506 be a date which is not earlier than the expiration date of the '012 patent.

24. Watson had knowledge of the '012 patent when it submitted ANDA No. 202506 to the FDA.

25. Upon information and belief, Watson intends to engage in the manufacture, use, offer for sale, sale, and/or importation of the Watson ANDA Products with the proposed labeling. The use of Watson's ANDA Products in accordance with and as directed by Watson's proposed labeling would infringe each of claims 25 and 26 of the '012 patent.

26. Upon information and belief, Watson intends to actively induce infringement of one or more claims of the '012 patent.

27. Upon information and belief, Watson knows that the Watson ANDA Products and the proposed labeling are especially made or adapted for use in infringing each of claims 25 and 26 of the '012 patent and that the ANDA Products and the proposed labeling are not suitable for any substantial noninfringing use.

28. Upon information and belief, Watson intends to contribute to the infringement of each of claims 25 and 26 of the '012 patent.

29. The foregoing actions by Watson constitute and/or would constitute infringement of each of claims 25 and 26 of the '012 patent, active inducement of infringement of each of claims 25 and 26 of the '012 patent, and/or contribution to the infringement by others of each of claims 25 and 26 of the '012 patent.

30. Pfizer will be substantially and irreparably harmed if Watson is not enjoined from infringing the '012 patent. Pfizer has no adequate remedy at law.

PRAYER FOR RELIEF

WHEREFORE, Pfizer requests the following relief:

A. A judgment that Watson's submission of ANDA No. 202506 was an act of infringement and that Watson's making, using, offering to sell, selling or importing the Watson ANDA Products prior to the expiration of the '012 patent will infringe, actively induce infringement and/or contribute to the infringement of the '012 patent;

B. A judgment that the effective date of any FDA approval for Watson to make, use offer for sale, sell, market, distribute, or import the Watson ANDA Products be no earlier than the expiration of the '012 patent;

C. A permanent injunction enjoining Watson, its officers, agents, servants, and employees, and those persons in active concert or participation with any of them, from making using, selling, offering for sale, marketing, distributing, or importing the Watson ANDA Products, and from inducing or contributing to any of the foregoing, prior to the expiration of the '012 patent;

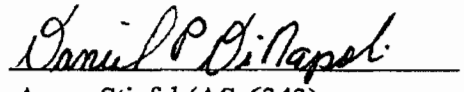
D. A judgment that this case is an exceptional case under 35 U.S.C. § 285, entitling Pfizer to an award of its reasonable attorneys' fees for bringing and prosecuting this action;

E. An award of Pfizer's costs and expenses in this action;

F. Such further and additional relief as this Court deems just and proper.

DATED: June 1, 2011

Respectfully submitted,



Aaron Stiefel (AS-6343)
Daniel DiNapoli (DD-4790)
Soumitra Deka (SD-7406)
Marc Zubick (MZ-1045)
KAYE SCHOLER LLP
425 Park Avenue
New York, NY 10022
(212) 836-8000 telephone
(212) 836-8689 facsimile
astiefel@kayescholer.com
ddinapoli@kayescholer.com
sdeka@kayescholer.com
mzubick@kayescholer.com

Attorneys for Plaintiffs Pfizer Inc., Pfizer Limited, and Pfizer Ireland Pharmaceuticals

EXHIBIT A

US006469012B1

(12) **United States Patent**
Ellis et al.

(10) **Patent No.: US 6,469,012 B1**
(45) **Date of Patent: Oct. 22, 2002**

(54) **PYRAZOLOPYRIMIDINONES FOR THE TREATMENT OF IMPOTENCE**

(75) Inventors: **Peter Ellis**; **Nicholas Kenneth Terrett**, both of Sandwich (GB)

(73) Assignee: **Pfizer Inc**, New York, NY (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **08/549,792**

(22) PCT Filed: **May 13, 1994**

(86) PCT No.: **PCT/EP94/01580**

§ 371 (c)(1),
(2), (4) Date: **Mar. 4, 1996**

(87) PCT Pub. No.: **WO94/28902**

PCT Pub. Date: **Dec. 22, 1994**

(30) **Foreign Application Priority Data**

Jun. 9, 1993 (GB) 9311920

(51) **Int. Cl.**[7] **A61K 31/519**; A61P 15/10
(52) **U.S. Cl.** **514/258**; 514/929
(58) **Field of Search** 514/258, 929

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Judgment of Nov. 8, 2000.

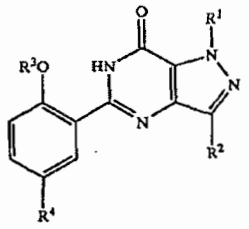
(List continued on next page.)

Primary Examiner—Edward J. Webman
(74) *Attorney, Agent, or Firm*—Peter C. Richardson; Gregg C. Benson; James T. Jones

(57) **ABSTRACT**

The use of a compound of formula (I)

(I)



wherein R^1 is H; C_1–C_3 alkyl; C_1–C_3 perfluoroalkyl; or C_3–C_5 cycloalkyl; R^2 is H; optionally substituted C_1–C_6 alkyl; C_1–C_3 perfluoroalkyl; or C_3–C_6 cycloalkyl; R^3 is optionally substituted C_1–C_6 alkyl; C_1–C_6 perfluoroalkyl; C_3–C_5 cycloalkyl; C_3–C_6 alkenyl; or C_3–C_6 alkynyl; R^4 is optionally substituted C_1–C_4 alkyl, C_2–C_4 alkenyl, C_2–C_4 alkanoyl, (hydroxy)C_2–C_4 alkyl or (C_2–C_3 alkoxy)C_1–C_2 alkyl; $CONR^5R^6$; CO_2R^7; halo; NR^5R^6; $NHSO_2NR^5R^6$; $NHSO_2R^8$; $SO_2NR^9R^{10}$; or phenyl, pyridyl, pyrimidinyl, imidazolyl, oxazolyl, thiazolyl, thienyl or triazolyl any of which is optionally substituted with methyl; R^5 and R^6 are each independently H or C_1–C_4 alkyl, or together with the nitrogen atom to which they are attached form an optionally substituted pyrrolidinyl, piperidino, morpholino, 4-N(R^{11})-piperazinyl or imidazolyl group; R^7 is H or C_1–$C_{4\ alkyl;\ R}{}^8$ is optionally substituted C_1–C_3 alkyl; R^9 and R^{10} together with the nitrogen atom to which they are attached form an optionally substituted pyrrolidinyl, piperidino, morpholino or 4-N(R^{12})-piperazinyl group; R^{11} is H; optionally substituted C_1–C_3 alkyl; (hydroxy)C_2–C_3 alkyl; or C_1–C_4 alkanoyl; R^{12} is H; optionally substituted C_1–C_6 alkyl; $CONR^{13}R^{14}$; $CSNR^{13}R^{14}$; or $C(NH)NR^{13}R^{14}$; and R?13? and R^{14} are each independently H; C_1–C_4 alkyl; or substituted C_2–C_4 alkyl; or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man; a pharmaceutical composition for said treatment; and a method of said treatment of said male animal with said pharmaceutical composition or with said either entity.

26 Claims, No Drawings

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PYRAZOLOPYRIMIDINONES FOR THE TREATMENT OF IMPOTENCE

This is a National Phase filing under 35 USC §371 based on PCT/EP94/01580, which was filed internationally on May 13, 1994.

This invention relates to the use of a series of pyrazolo [4,3-d]pyrimidin-7-ones for the treatment of impotence.

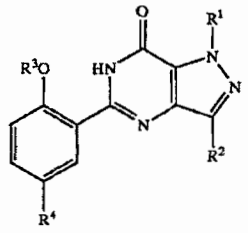
Impotence can be defined literally as a lack of power, in the male, to copulate and may involve an inability to achieve penile erection or ejaculation, or both. More specifically, erectile impotence or dysfunction may be defined as an inability to obtain or sustain an erection adequate for intercourse. Its prevalence is claimed to be between 2 and 7% of the human male population, increasing with age, up to 50 years, and between 18 and 75% between 55 and 80 years of age. In the USA alone, for example, it has been estimated that there are up to 10 million impotent males, with the majority suffering from problems of organic rather than of psychogenic origin.

Reports of well-controlled clinical trials in man are few and the efficacy of orally administered drugs is low. Although many different drugs have been shown to induce penile erection, they are only effective after direct injection into the penis, e.g. intraurethrally or intracavernosally (i.c.), and are not approved for erectile dysfunction. Current medical treatment is based on the i.c injection of vasoactive substances and good results have been claimed with phenoxybenzamine, phentolamine, papaverine and prostaglandin E_1, either alone or in combination; however, pain, priapism and fibrosis of the penis are associated with the i.c. administration of some of these agents. Potassium channel openers (KCO) and vasoactive intestinal polypeptide (VIP) have also been shown to be active i.c., but cost and stability issues could limit development of the latter. An alternative to the i.c. route is the use of glyceryl trinitrate (GTN) patches applied to the penis, which has been shown to be effective but produces side-effects in both patient and partner.

As a general alternative to pharmacological intervention, a variety of penile prostheses has been used to assist achievement of an erection. The short term success rate is good, but problems with infection and ischaemia, especially in diabetic men, make this type of treatment a final option rather than first-line therapy.

The compounds of the invention are potent inhibitors of cyclic guanosine 3',5'-monophosphate phosphodiesterases (cGMP PDEs) in contrast to their inhibition of cyclic adenosine 3',5'-monophosphate phosphodiesterases (cAMP PDEs). This selective enzyme inhibition leads to elevated cGMP levels which, in turn, provides the basis for the utilities already disclosed for the said compounds in EP-A-0463756 and EP-A-0526004, namely in the treatment of stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, conditions of reduced blood vessel patency e.g. post-percutaneous transluminal coronary angioplasty (post-PTCA), peripheral vascular disease, stroke, bronchitis, allergic asthma, chronic asthma, allergic rhinitis, glaucoma, and diseases characterised by disorders of gut motility, e.g. irritable bowel syndrome (IBS).

Unexpectedly, it has now been found that these disclosed compounds are useful in the treatment of erectile dysfunction. Furthermore the compounds may be administered orally, thereby obviating the disadvantages associated with i.c. administration. Thus the present invention concerns the use of a compound of formula (I):



(I)

wherein

R^1 is H; C_1–C_3 alkyl; C_1–C_3 perfluoroalkyl; or C_3–C_5 cycloalkyl;

R^2 is H; C_1–C_6 alkyl optionally substituted with C_3–C_6 cycloalkyl; C_1–C_3 perfluoroalkyl; or C_3–C_6 cycloalkyl;

R^3 is C_1–C_6 alkyl optionally substituted with C_3–C_6 cycloalkyl; C_1–C_6 perfluoroalkyl; C_3–C_5 cycloalkyl; C_3–C_6 alkenyl; or C_3–C_6 alkynyl;

R^4 is C_1–C_4 alkyl optionally substituted with OH, NR^5R^6, CN, $CONR^5R^6$ or CO_2R^7; C_2–C_4 alkenyl optionally substituted with CN, $CONR^5R^6$ or CO_2R^7; C_2–C_4 alkanoyl optionally substituted with NR^5R^6; (hydroxy)C_2–C_4 alkyl optionally substituted with NR^5R^6; (C_2–C_3 alkoxy)C_1–C_2 alkyl optionally substituted with OH or NR^5R^6; $CONR^5R^6$; CO_2R^7; halo; NR^5R^6; $NHSO_2NR^5R^6$; $NHSO_2R^8$; $SO_2NR^9R^{10}$; or phenyl, pyridyl, pyrimidinyl, imidazolyl, oxazolyl, thiazolyl, thienyl or triazolyl any of which is optionally substituted with methyl;

R^5 and R^6 are each independently H or C_1–C_4 alkyl, or together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, morpholino, 4-N(R^{11})-piperazinyl or imidazolyl group wherein said group is optionally substituted with methyl or OH;

R^7 is H or C_1–C_4 alkyl;

R^8 is C_1–C_3 alkyl optionally substituted with NR^5R^6;

R^9 and R^{10} together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, morpholino or 4-N(R^{12})-piperazinyl group wherein said group is optionally substituted with C_1–C_4 alkyl, C_1–C_3 alkoxy, $NR^{13}R^{14}$ or $CONR^{13}R^{14}$;

R^{11} is H; C_1–C_3 alkyl optionally substituted with phenyl; (hydroxy)C_2–C_3 alkyl; or C_1–C_4 alkanoyl;

R^{12} is H; C_1–C_6 alkyl; (C_1–C_3 alkoxy)C_2–C_6 alkyl; (hydroxy)C_2–C_6 alkyl; ($R^{13}R^{14}N$)C_2–C_6 alkyl; ($R^{13}R^{14}NOC$)C_1–C_6 alkyl; $CONR^{13}R^{14}$; $CSNR^{13}R^{14}$; or $C(NH)NR^{13}R^{14}$; and

R^{13} and R^{14} are each independently H; C_1–C_4 alkyl; (C_1–C_3 alkoxy)C_2–C_4 alkyl; or (hydroxy)C_2–C_4 alkyl;

or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man.

In the above definition, unless otherwise indicated, alkyl groups having three or more carbon atoms, alkenyl and alkynyl groups having four or more carbon atoms, alkoxy groups having three carbon atoms and alkanoyl groups having four carbon atoms may be straight chain or branched chain. Halo means fluoro, chloro, bromo or iodo.

The compounds of formula (I) may contain one or more asymmetric centres and thus they can exist as enantiomers or

diastereoisomers. Furthermore, certain compounds of formula (I) which contain alkenyl groups may exist as cis-isomers or trans-isomers. In each instance, the invention includes both mixtures and separate individual isomers.

The compounds of formula (I) may also exist in tautomeric forms and the invention includes both mixtures and separate individual tautomers.

The pharmaceutically acceptable salts of the compounds of formula (I) which contain a basic centre are, for example, non-toxic acid addition salts formed with inorganic acids such as hydrochloric, hydrobromic, sulphuric and phosphoric acid, with organo-carboxylic acids, or with organo-sulphonic acids. Compounds of formula (I) can also provide pharmaceutically acceptable metal salts, in particular non-toxic alkali metal salts, with bases. Examples include the sodium and potassium salts.

A preferred group of compounds of formula (I) is that wherein R^1 is H, methyl or ethyl; R^2 is C_1–C_3 alkyl; R^3 is C_2–C_3 alkyl or allyl; R^4 is C_1–C_2 alkyl optionally substituted with OH, NR^5R^6, CN, $CONR^5R^6$ or CO_2R^7; acetyl optionally substituted with NR^5R^6; hydroxyethyl optionally substituted with NR^5R^6; ethoxymethyl optionally substituted with OH or NR^5R^6; $CH{=}CHCN$; $CH{=}CHCONR^5R^6$; $CH{=}CHCO_2R^7$; $CONR^5R^6$; CO_2H; Br; NR^5R^6; $NHSO_2NR^5R^6$; $NHSO_2R^8$; $SO_2NR^9R^{10}$; or pyridyl or imidazolyl either of which is optionally substituted with methyl; R^5 and R^6 are each independently H, methyl or ethyl, or together with the nitrogen atom to which they are attached form a piperidino, morpholino, 4-N(R^{11})-piperazinyl or imidazolyl group wherein said group is optionally substituted with methyl or OH; R^7 is H or t-butyl; R^8 is methyl or $CH_2CH_2CH_2NR^5R^6$; R^9 and R^{10} together with the nitrogen atom to which they are attached form a piperidino or 4-N(R^{12})-piperazinyl group wherein said group is optionally substituted with $NR^{13}R^{14}$ or $CONR^{13}R^{14}$; R^{11} is H, methyl, benzyl, 2-hydroxyethyl or acetyl; R^{12} is H, C_1–C_3 alkyl, (hydroxy)C_2–C_3 alkyl, $CSNR^{13}R^{14}$ or $C(NH)NR^{13}R^{14}$; and R^{13} and R^{14} are each independently H or methyl.

A more preferred group of compounds of formula (I) is that wherein R^1 is methyl or ethyl; R^2 is C_1–C_3 alkyl; R^3 is ethyl, n-propyl or allyl; R^4 is $CH_2NR^5R^6$, $COCH_2NR^5R^6$, $CH(OH)CH_2NR^5R^6$, $CH_2OCH_2CH_3$, $CH_2OCH_2CH_2OH$, $CH_2OCH_2CH_2NR^5R^6$, $CH{=}CHCON(CH_3)_2$, $CH{=}CHCO_2R^7$, $CONR^5R_6$, CO_2H, Br, $NHSO_2NR^5R^6$, $NHSO_2CH_2CH_2CH_2NR^5R^6$, $SO_2NR^9R^{10}$, 2-pyridyl, 1-imidazolyl or 1-methyl-2-imidazolyl; R^5 and R^6 together with the nitrogen atom to which they are attached form a piperidino, 4-hydroxypiperidino, morpholino, 4-N(R^{11})-piperazinyl or 2-methyl-1-imidazolyl group; R^7 is H or t-butyl; R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4-carbamoylpiperidino or 4-N(R^{12})-piperazinyl group; R^{11} is H, methyl, benzyl, 2-hydroxyethyl or acetyl; and R^{12} is H, C_1–C_3 alkyl, 2-hydroxyethyl or $CSNH_2$.

A particularly preferred group of compounds of formula (I) is that wherein R^1 is methyl or ethyl; R^2 is n-propyl; R^3 is ethyl, n-propyl or allyl; R^4 is $COCH_2NR^5R^6$, $CONR^5R^6$, $SO_2NR^9R^{10}$ or 1-methyl-2-imidazolyl; R^5 and R^6 together with the nitrogen atom to which they are attached form a morpholino or 4-N(R^{11})-piperazinyl group; R^9 and R_{10} together with the nitrogen atom to which they are attached form a 4-N(R^{12})-piperazinyl group; R^{11} is methyl or acetyl; and R^{12} is H, methyl, 2-propyl or 2-hydroxyethyl.

Especially preferred individual compounds of the invention include:

5-(2-ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1, 6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-(5-morpholinoacetyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1, 6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[2-allyloxy-5-(4-methyl-1-piperazinylsulphonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-{2-ethoxy-5-[4-(2-propyl)-1-piperazinyl-sulphonyl]phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-{2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinyl-sulphonyl]phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-{5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]-2-n-propoxyphenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[2-ethoxy-5-(4-methyl-1-piperazinylcarbonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one; and

5-[2-ethoxy-5-(1-methyl-2-imidazolyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

The compounds of formula (I) and their pharmaceutically acceptable salts, processes for the preparation thereof, in vitro test methods for determining the cGMP PDE and cAMP PDE inhibitory activities thereof, pharmaceutical compositions thereof and routes of administration for human use, are described in EP-A-0463756 and EP-A-0526004.

A preliminary investigation was carried out with a view to isolating and characterising the cyclic nucleotide PDEs of human corpus cavernosum, relaxation of which leads to penile erection. Studies of substrate specificity, response to activators and inhibitor sensitivity, have demonstrated that human corpus cavernosum contains three distinct PDE enzymes.

METHODS

Fresh frozen human penis was obtained from IIAM (Pennsylvania). Tissue was thawed at room temperature, the corpus cavernosum was dissected from the penis to yield approximately 2–4 g of tissue and the following isolation protocol was followed. Tissue was coarsely chopped in ice-cold isotonic buffer (35 ml) containing 250 mM sucrose, 1 mM EDTA, 0.5 mM PMSF and 20 mM HEPES, pH 7.2, and the mixture subjected to brief (1 min.) treatment with a Silversen mixer/emulsifier. Homogenates were prepared using homogeniser tubes with teflon pestles and soluble fraction was prepared by centrifugation at 100,000xg for 60 min. at 4° C. 10 ml of high speed supernatant was applied to a Pharmacia Mono Q anion exchange column (1 ml bed volume) equilibrated with buffer containing 1 mM EDTA, 0.5 mM PMSF and 20 mM lhEPES, pH 7.2 (chromatography buffer). The column was then washed with 5 bed volumes of chromatography buffer, after which PDEs were eluted using a continuous gradient of 0–500 mM NaCl (total volume 35 ml) and 1 ml fractions collected.

Column fractions were assayed for PDE activity using 500 nM cGMP or 500 nM cAMP as substrate. cAMP PDE activity was also determined in the presence of 1 μM unlabelled cGMP and the PDE activity of selected fractions was determined in the presence of 10 mM $CaCl_2$ and 10 units/ml bovine brain calmodulin. Appropriate fractions were pooled and stored at 4° C. during the course of the study.

Inhibition studies were performed using a substrate concentration of 500 nM throughout. All inhibitors were dissolved in DMSO and concentration-response curves were constructed over the range 3×10^{-10} to 1×10^{-4} M in half log increments. IC_{50} values were calculated using the sigmoidal curve fitting algorithm of biostat.

RESULTS

Human corpus cavernosum soluble PDEs were separated into three distinct fractions of activity. The first, fraction I, (designated by order of elution) represents the major PDE present and is highly selective for cGMP as substrate. This fraction was found to be insensitive to stimulation by calcium/calmodulin and was classified as PDE_V. Fraction II hydrolyses cGMP and cAMP, with the latter activity being stimulated in the presence of cGMP, and is classified as PDE_{II}, whilst fraction III is cAMP selective and this activity is inhibited in the presence of cGMP, consistent with PDE_{III} activity.

In order to further characterise the PDE isoenzymes present in the tissue, studies were performed using a variety of inhibitors. Inhibitor studies with fractions I and II were performed using cGMP as substrate, whilst fraction III studies utilised cAMP. These studies confirmed that fraction I corresponds to PDE_V, whilst fraction III was clearly identified as PDE_{III}; fraction II (PDE_{II}) was relatively insensitive to all the inhibitors tested.

In summary, the above investigation identified three PDE isoenzymes in human corpus cavernosum tissue. The predominant PDE is the cGMP-specific PDE_V, whilst cGMP-stimulated cAMP PDE_{II} and cGMP-inhibited cAMP PDE_{III} are also present.

The compounds of the invention have been tested in vitro and found to be potent and selective inhibitors of the cGMP-specific PDE_V. For example, one of the especially preferred compounds of the invention has an IC_{50}=6.8 nM v. the PDE_V enzyme, but demonstrates only weak inhibitory activity against the PDE_{II} and PDE_{III} enzymes with IC_{50}= >100 μM and 34 μM respectively. Thus relaxation of the corpus cavernosum tissue and consequent penile erection is presumably mediated by elevation of cGMP levels in the said tissue, by virtue of the PDE inhibitory profile of the compounds of the invention.

Furthermore, none of the compounds of the invention tested in rat and dog, both intravenously (i.v.) and orally (p.o.) at up to 3 mg/Kg, has shown any overt sign of adverse acute toxicity. In mouse, no deaths occurred after doses of up to 100 mg/Kg i.v. Certain especially preferred compounds showed no toxic effects on chronic p.o. administration to rat at up to 10 mg/Kg and to dog at up to 20 mg/Kg.

In man, certain especially preferred compounds have been tested orally in both single dose and multiple dose volunteer studies. Moreover, patient studies conducted thus far have confirmed that one of the especially preferred compounds induces penile erection in impotent males.

Although the compounds of the invention are envisaged primarily for the treatment of erectile dysfunction or sexual dysfunction, they may also be useful for the treatment of female sexual dysfunction including orgasmic dysfunction related to clitoral disturbances.

Generally, in man, oral administration of the compounds of the invention is the preferred route, being the most convenient and avoiding the disadvantages associated with i.c. administration. A preferred dosing regimen for a typical man is 5 to 75 mg of compound three times daily. In circumstances where the recipient suffers from a swallowing disorder or from impairment of drug absorption after oral administration, the drug may be administered parenterally, e.g. sublingually or buccally.

For veterinary use, a compound of formula (I) or a non-toxic salt thereof is administered as a suitably acceptable formulation in accordance with normal veterinary practice and the veterinary surgeon will determine the dosing regimen and route of administration which will be most appropriate for a particular male animal.

Thus the invention includes a pharmaceutical composition for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man, comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

There is further provided a process for the preparation of a pharmaceutical composition for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man, comprising formulating a compound of formula (I), or a pharmaceutically acceptable salt thereof, with a pharmaceutically acceptable diluent or carrier.

The invention also provides a method of treating a male animal, including man, to cure or prevent erectile dysfunction which comprises treating said male animal with an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity.

In a further aspect, the invention includes the use of a cGMP PDE inhibitor, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the oral treatment of erectile dysfunction in man.

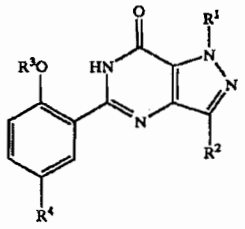
The invention also includes a method of orally treating man to cure or prevent erectile dysfunction, which comprises treatment with an orally effective amount of a cGMP PDE inhibitor, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity.

Moreover, the invention includes the use of a cGMP PDE inhibitor, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic oral treatment of erectile dysfunction in man.

What is claimed is:

1. A method of treating erectile dysfunction in a male animal, comprising administering to a male animal in need of such treatment an effective amount of a compound of formula (I):

(I)



wherein:

R^1 is H; C_1–C_3 alkyl; C_1–C_3 perfluoroalkyl; or C_3–C_5 cycloalkyl;

R^2 is H; C_1–C_6 alkyl optionally substituted with C_3–C_6 cycloalkyl; C_1–C_3 perfluoroalkyl; or C_3–C_6 cycloalkyl;

R^3 is C_1–C_6 alkyl optionally substituted with C_3–C_6 cycloalkyl; C_1–C_6 perfluoroalkyl; C_3–C_5 cycloalkyl; C_3–C_6 alkenyl; or C_3–C_6 alkynyl;

R^4 is C_1–C_4 alkyl optionally substituted with OH, NR^5R^6, CN, $CONR^5R^6$ or CO_2R^7; C_2–C_4 alkenyl optionally substituted with CN, $CONR_5R^6$ or CO_2R^7; C_2–C_4 alkanoyl optionally substituted with NR^5R^6; (hydroxy) C_2–C_4 alkyl optionally substituted with NR^5R^6; (C_2–C_3 alkoxy)C_1–C_2 alkyl optionally substituted with OH or NR^5R^6; $CONR^5R^6$; CO_2R^7; halo; NR^5R^6; $NHSO_2NR^5R^6$; $NHSO_2R^8$; $SO_2NR^9R^{10}$; or phenyl pyridyl, pyrimidinyl, imidazolyl, oxazolyl, thiazolyl, thienyl or triazolyl any of which is optionally substituted with methyl;

R^5 and R^6 are each independently H or C_1–C_4 alkyl, or together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, morpholino, 4-N(R^{11})-piperazinyl or imidazolyl group wherein said group is optionally substituted with methyl or OH;

R^7 is H or C_1–C_4 alkyl;

R^8 is C_1–C_3 alkyl optionally substituted with NR^5R^6;

R^9 and R^{10} together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, morpholino or 4-N(R^{12})-piperazinyl group wherein said group is optionally substituted with C_1–C_4 alkyl, C_1–C_3 alkoxy, $NR^{13}R^{14}$ or $CONR^{13}R^{14}$;

R^{11} is H; C_1–C_3 alkyl optionally substituted with phenyl; (hydroxy)C_2–C_3 alkyl; or C_1–C_4 alkanoyl;

R^{12} is H; C_1–C_6 alkyl; (C_1–C_3 alkoxy)C_2–C_6 alkyl; (hydroxy)C_2–C_6 alkyl; ($R^{13}R^{14}N$)C_2–C_6 alkyl; ($R^{13}R^{14}NOC$)C_1–C_6 alkyl; $CONR^{13}R^{14}$; $CSNR^{13}R^{14}$; or $C(NH)NR^{13}R^{14}$; and

R^{13} and R^{14} are each independently H; C_1–C_4 alkyl; (C_1–C_3 alkoxy)C_2–C_4 alkyl; or (hydroxy)C_2–C_4 alkyl;

or a pharmaceutically acceptable salt thereof;

or a pharmaceutically acceptable composition containing either entity.

2. A method as defined in claim **1**, wherein said treatment is veterinary treatment.

3. A method as defined in claim **1**, wherein said compound is 5-(2-ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

4. A method as defined in claim **1**, wherein said compound is 5-[2-ethoxy-5-(4-methyl-1-piperazinyl-sulphonyl) phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

5. A method as defined in claim **1**, wherein said compound, salt or composition is administered orally, intravenously, sublingually, or buccally.

6. A method as defined in claim **1**, wherein said compound, salt or composition is administered orally.

7. A method as defined in claim **6** wherein in the compound of formula (I) R^1 is H, methyl or ethyl; R^2 is C_1–C_3 alkyl; R^3 is C_2–C_3 alkyl or allyl; R^4 is C_1–C_2 alkyl optionally substituted with OH, NR^5R^6, CN, $CONR^5R^6$ or CO_2R^7; acetyl optionally substituted with NR^5R^6; hydroxyethyl optionally substituted with NR^5R^6; ethoxymethyl optionally substituted with OH or NR^5R^6; CH=CHCN; $CH=CHCONR^5R^6$; $CH=CHCO_2R^7$; $CONR^5R^6$; CO_2H; Br; NR^5R^6; $NHSO_2NR^5R^6$; $NHSO_2R^8$; $SO_2NR^9R^{10}$; or pyridyl or imidazolyl either of which is optionally substituted with methyl; R^5 and R^6 are each independently H, methyl or ethyl, or together with the nitrogen atom to which they are attached form a piperidino, morpholino, 4-N(R^{11})-piperazinyl or imidazolyl group wherein said group is optionally substituted with methyl or OH; R^7 is H or t-butyl; R^8 is methyl or $CH_2CH_2CH_2NR^5R^6$; R^9 and R^{10} together with the nitrogen atom to which they are attached form a piperidino or 4-N(R^{12})-piperazinyl group wherein said group is optionally substituted with $NR^{13}R^{14}$ or $CONR^{13}R^{14}$; R^{11} is H, methyl, benzyl, 2-hydroxyethyl or acetyl; R^{12} is H, C_1–C_3 alkyl, (hydroxy)C_2–C_3 alkyl, $CSNR^{13}R^{14}$ or $C(NH)NR^{13}R^{14}$; and R^{13} and R^{14} are each independently H or methyl.

8. A method as defined in claim **7** wherein in the compound of formula (I) R^1 is methyl or ethyl; R^2 is C_1–C_3 alkyl; R^3 is ethyl, n-propyl or allyl; R^4 is $CH_2NR^5R^6$, $COCH_2NR^5R^6$, $CH(OH)CH_2NR^5R^6$, $CH_2OCH_2CH_3$, $CH_2OCH_2CH_2OH$, $CH_2OCH_2CH_2NR^5R^6$, CH=CHCON$(CH_3)_2$, $CH=CHCO_2R^7$, $CONR^5R^6$, CO_2H, Br, $NHSO_2NR^5R^6$, $NHSO_2CH_2CH_2CH_2NR^5R^6$, $SO_2NR^9R^{10}$, 2-pyridyl, 1-imidazolyl or 1-methyl-2-imidazolyl; R^5 and R^6 together with the nitrogen atom to which they are attached form a piperidino, 4-hydroxypiperidino, morpholino, 4-N(R^{11})-piperazinyl or 2-methyl-1-imidazolyl group; R^7 is H or t-butyl; R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4-carbamoylpiperidino or 4-N(R^{12})-piperazinyl group; R^{11} is H, methyl, benzyl, 2-hydroxyethyl or acetyl; and R^{12} is H, C_1–C_3 alkyl, 2-hydroxyethyl or $CSNH_2$.

9. A method as defined in claim **8** wherein in the compound of formula (I) R^1 is methyl or ethyl; R^2 is n-propyl; R^3 is ethyl, n-propyl or allyl; R^4 is $COCH_2NR^5R^6$, $CONR^5R^6$, $SO_2NR^9R^{10}$ or 1-methyl-2-imidazolyl; R^5 and R^6 together with the nitrogen atom to which they are attached form a morpholino or 4-N(R^{11})-piperazinyl group; R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4-N(R^{12})-piperazinyl group; R^{11} is methyl or acetyl; and R^{12} is H, methyl, 2-propyl or 2-hydroxyethyl.

10. A method as defined in claim **9** wherein the compound of formula (I) is selected from:

5-(2-ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-(5-morpholinoacetyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d] pyrimidin-7-one;

5-[2-allyloxy-5-(4-methyl-1-piperazinylsulphonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo [4,3-d]pyrimidin-7-one;

5-{2-ethoxy-5-[4-(2-propyl)-1-piperazinyl-sulphonyl] phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo [4,3-d]pyrimidin-7-one;

5-{2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinyl-sulphonyl]phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-{5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]-2-n-propoxyphenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[2-ethoxy-5-(4-methyl-1-piperazinylcarbonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d] pyrimidin-7-one; and

5-[2-ethoxy-5-(1-methyl-2-imidazolyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

11. A method as defined in claim **10** wherein the compound of formula (I) is 5-(2-ethoxy-5-morpholino-acetylphenyl)-1-methyl-3-n-ptopyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

12. A method as defined in claim **10** wherein the compound of formula (I) is 5-(5-morpholinoacetyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

13. A method as defined in claim **10** wherein the compound of formula (I) is 5-[2-ethoxy-5-(4-methyl-1-

piperazinylsulphonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

14. A method as defined in claim 10 wherein the compound of formula (I) is 5-[2-allyloxy-5-(4-methyl-1-piperazinylsulphonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

15. A method as defined in claim 10 wherein the compound of formula (I) is 5-{2-ethoxy-5-[4-(2-propyl)-1-piperazinyl-sulphonyl]phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

16. A method as defined in claim 10 wherein the compound of formula (I) is 5-{2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinyl-sulphonyl]phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

17. A method as defined in claim 10 wherein the compound of formula (I) is 5-{5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]-2-n-propoxyphenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

18. A method as defined in claim 10 wherein the compound of formula (I) is 5-[2-ethoxy-5-(4-methyl-1-piperazinylcarbonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

19. A method as defined in claim 10 wherein the compound of formula (I) is 5-[2-ethoxy-5-(1-methyl-2-imidazolyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

20. A method as defined in claim 6, wherein said animal is a human.

21. A method as defined in claim 1, wherein said compound, salt or composition is administered intravenously.

22. A method as defined in claim 1, wherein said compound, salt or composition is administered sublingually.

23. A method as defined in claim 1, wherein said compound, salt or composition is administered buccally.

24. A method of treating erectile dysfunction in a male human, comprising orally administering to a male human in need of such treatment an effective amount of a selective cGMP PDE$_5$ inhibitor, or a pharmaceutically acceptable salt thereof, of a pharmaceutical composition containing either entity.

25. A method of treating erectile dysfunction in a male human, comprising orally administering to a male human in need of such treatment an effective amount of a compound selected from:

5-(2-ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-(5-morpholinoacetyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[2-allyloxy-5-(4-methyl-1-piperazinylsulphonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-{2-ethoxy-5-[4-(2-propyl)-1-piperazinyl-sulphonyl]phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-{2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinyl-sulphonyl]phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-{5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]-2-n-propoxyphenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[2-ethoxy-5-(4-methyl-1-piperazinylcarbonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one; and

5-[2-ethoxy-5-(1-methyl-2-imidazolyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

or a pharmaceutically acceptable salt thereof;

or a pharmaceutical composition containing either entity.

26. A method as defined in claim 25, wherein said compound is 5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity.

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JS 44C/SDNY
REV. 5/2010

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11 CV 3721

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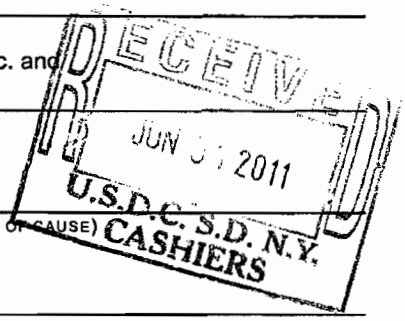

PLAINTIFFS	DEFENDANTS
Pfizer Inc., Pfizer Limited, and Pfizer Ireland Pharmaceuticals	Watson Pharmaceuticals, Inc. and Watson Laboratories, Inc.
ATTORNEYS (FIRM NAME, ADDRESS, AND TELEPHONE NUMBER	ATTORNEYS (IF KNOWN)
KAYE SCHOLER LLP., 425 PARK AVENUE, NEW YORK, NEW YORK (212)836-8000	

CAUSE OF ACTION (CITE THE U.S. CIVIL STATUTE UNDER WHICH YOU ARE FILING AND WRITE A BRIEF STATEMENT OF CAUSE)
(DO NOT CITE JURISDICTIONAL STATUTES UNLESS DIVERSITY)

U.S.C. Title 35 - Patent Infringement.

Has this or a similar case been previously filed in SDNY at any time? No? ☑ Yes? ☐ Judge Previously Assigned

If yes, was this case Vol. ☐ Invol. ☐ Dismissed. No ☐ Yes ☐ If yes, give date _____ & Case No. _____

(PLACE AN [x] IN ONE BOX ONLY) NATURE OF SUIT

CONTRACT
[ ] 110 INSURANCE
[ ] 120 MARINE
[ ] 130 MILLER ACT
[ ] 140 NEGOTIABLE INSTRUMENT
[ ] 150 RECOVERY OF OVERPAYMENT & ENFORCEMENT OF JUDGMENT
[ ] 151 MEDICARE ACT
[ ] 152 RECOVERY OF DEFAULTED STUDENT LOANS (EXCL VETERANS)
[ ] 153 RECOVERY OF OVERPAYMENT OF VETERAN'S BENEFITS
[ ] 160 STOCKHOLDERS SUITS
[ ] 190 OTHER CONTRACT
[ ] 195 CONTRACT PRODUCT LIABILITY
[ ] 196 FRANCHISE

REAL PROPERTY
[ ] 210 LAND CONDEMNATION
[ ] 220 FORECLOSURE
[ ] 230 RENT LEASE & EJECTMENT
[ ] 240 TORTS TO LAND
[ ] 245 TORT PRODUCT LIABILITY
[ ] 290 ALL OTHER REAL PROPERTY

TORTS

PERSONAL INJURY
[ ] 310 AIRPLANE
[ ] 315 AIRPLANE PRODUCT LIABILITY
[ ] 320 ASSAULT, LIBEL & SLANDER
[ ] 330 FEDERAL EMPLOYERS' LIABILITY
[ ] 340 MARINE
[ ] 345 MARINE PRODUCT LIABILITY
[ ] 350 MOTOR VEHICLE
[ ] 355 MOTOR VEHICLE PRODUCT LIABILITY
[ ] 360 OTHER PERSONAL INJURY

PERSONAL INJURY
[ ] 362 PERSONAL INJURY - MED MALPRACTICE
[ ] 365 PERSONAL INJURY PRODUCT LIABILITY
[ ] 368 ASBESTOS PERSONAL INJURY PRODUCT LIABILITY

PERSONAL PROPERTY
[ ] 370 OTHER FRAUD
[ ] 371 TRUTH IN LENDING
[ ] 380 OTHER PERSONAL PROPERTY DAMAGE
[ ] 385 PROPERTY DAMAGE PRODUCT LIABILITY

ACTIONS UNDER STATUTES

CIVIL RIGHTS
[ ] 441 VOTING
[ ] 442 EMPLOYMENT
[ ] 443 HOUSING/ ACCOMMODATIONS
[ ] 444 WELFARE
[ ] 445 AMERICANS WITH DISABILITIES - EMPLOYMENT
[ ] 446 AMERICANS WITH DISABILITIES -OTHER
[ ] 440 OTHER CIVIL RIGHTS

PRISONER PETITIONS
[ ] 510 MOTIONS TO VACATE SENTENCE 20 USC 2255
[ ] 530 HABEAS CORPUS
[ ] 535 DEATH PENALTY
[ ] 540 MANDAMUS & OTHER
[ ] 550 CIVIL RIGHTS
[ ] 555 PRISON CONDITION

FORFEITURE/PENALTY
[ ] 610 AGRICULTURE
[ ] 620 OTHER FOOD & DRUG
[ ] 625 DRUG RELATED SEIZURE OF PROPERTY 21 USC 881
[ ] 630 LIQUOR LAWS
[ ] 640 RR & TRUCK
[ ] 650 AIRLINE REGS
[ ] 660 OCCUPATIONAL SAFETY/HEALTH
[ ] 690 OTHER

LABOR
[ ] 710 FAIR LABOR STANDARDS ACT
[ ] 720 LABOR/MGMT RELATIONS
[ ] 730 LABOR/MGMT REPORTING & DISCLOSURE ACT
[ ] 740 RAILWAY LABOR ACT
[ ] 790 OTHER LABOR LITIGATION
[ ] 791 EMPL RET INC SECURITY ACT

IMMIGRATION
[ ] 462 NATURALIZATION APPLICATION
[ ] 463 HABEAS CORPUS-ALIEN DETAINEE
[ ] 465 OTHER IMMIGRATION ACTIONS

ACTIONS UNDER STATUTES

BANKRUPTCY
[ ] 422 APPEAL 28 USC 158
[ ] 423 WITHDRAWAL 28 USC 157

PROPERTY RIGHTS
[ ] 820 COPYRIGHTS
[X] 830 PATENT
[ ] 840 TRADEMARK

SOCIAL SECURITY
[ ] 861 HIA (1395ff)
[ ] 862 BLACK LUNG (923)
[ ] 863 DIWC/DIWW (405(g))
[ ] 864 SSID TITLE XVI
[ ] 865 RSI (405(g))

FEDERAL TAX SUITS
[ ] 870 TAXES (U.S. Plaintiff or Defendant)
[ ] 871 IRS-THIRD PARTY 26 USC 7609

OTHER STATUTES
[ ] 400 STATE REAPPORTIONMENT
[ ] 410 ANTITRUST
[ ] 430 BANKS & BANKING
[ ] 450 COMMERCE
[ ] 460 DEPORTATION
[ ] 470 RACKETEER INFLUENCED & CORRUPT ORGANIZATION ACT (RICO)
[ ] 480 CONSUMER CREDIT
[ ] 490 CABLE/SATELLITE TV
[ ] 810 SELECTIVE SERVICE
[ ] 850 SECURITIES/ COMMODITIES/ EXCHANGE
[ ] 875 CUSTOMER CHALLENGE 12 USC 3410
[ ] 890 OTHER STATUTORY ACTIONS
[ ] 891 AGRICULTURAL ACTS
[ ] 892 ECONOMIC STABILIZATION ACT
[ ] 893 ENVIRONMENTAL MATTERS
[ ] 894 ENERGY ALLOCATION ACT
[ ] 895 FREEDOM OF INFORMATION ACT
[ ] 900 APPEAL OF FEE DETERMINATION UNDER EQUAL ACCESS TO JUSTICE
[ ] 950 CONSTITUTIONALITY OF STATE STATUTES

Check if demanded in complaint:

☐ CHECK IF THIS IS A CLASS ACTION UNDER F.R.C.P. 23

DO YOU CLAIM THIS CASE IS RELATED TO A CIVIL CASE NOW PENDING IN S.D.N.Y.? IF SO, STATE:

DEMAND $_____ OTHER _____ JUDGE Judge Thomas P. Greisa DOCKET NUMBER 1:10-cv-08197

Check YES only if demanded in complaint
JURY DEMAND: ☐ YES ☐ NO

NOTE: Please submit at the time of filing an explanation of why cases are deemed related.

See attached Addendum

(PLACE AN x IN ONE BOX ONLY) **ORIGIN**

☑ 1 Original Proceeding ☐ 2a. Removed from State Court ☐ 2b. Removed from State Court AND at least one party is pro se. ☐ 3 Remanded from Appellate Court ☐ 4 Reinstated or Reopened ☐ 5 Transferred from (Specify District) ☐ 6 Multidistrict Litigation ☐ 7 Appeal to District Judge from Magistrate Judge Judgment

(PLACE AN x IN ONE BOX ONLY) **BASIS OF JURISDICTION** ***IF DIVERSITY, INDICATE CITIZENSHIP BELOW. (28 USC 1322, 1441)***

☐ 1 U.S. PLAINTIFF ☐ 2 U.S. DEFENDANT ☑ 3 FEDERAL QUESTION (U.S. NOT A PARTY) ☐ 4 DIVERSITY

CITIZENSHIP OF PRINCIPAL PARTIES (FOR DIVERSITY CASES ONLY)

(Place an [X] in one box for Plaintiff and one box for Defendant)

	PTF	DEF		PTF	DEF		PTF	DEF
CITIZEN OF THIS STATE	[ ]1	[ ]1	CITIZEN OR SUBJECT OF A FOREIGN COUNTRY	[ ]3	[ ]3	INCORPORATED and PRINCIPAL PLACE OF BUSINESS IN ANOTHER STATE	[ ]5	[ ]5
CITIZEN OF ANOTHER STATE	[ ]2	[ ]2	INCORPORATED or PRINCIPAL PLACE OF BUSINESS IN THIS STATE	[ ]4	[ ]4	FOREIGN NATION	[ ]6	[ ]6

PLAINTIFF(S) ADDRESS(ES) AND COUNTY(IES)

Pfizer Inc.: 235 East 42 Street, New York, New York 10017
Pfizer Limited: Ramsgate Road, Sandwich, Kent, England
Pfizer Ireland Pharmaceuticals: Operations Support Group, Ringaskiddy, Co Cork, Republic of Ireland

DEFENDANT(S) ADDRESS(ES) AND COUNTY(IES)

Watson Pharmaceuticals, Inc.: Morris Corporate Center III, 400 Interpace Parkway, Parsippany, New Jersey 07054
Watson Laboratories, Inc.: 311 Bonnie Circle, Corona, California 92880

DEFENDANT(S) ADDRESS UNKNOWN
REPRESENTATION IS HEREBY MADE THAT, AT THIS TIME, I HAVE BEEN UNABLE, WITH REASONABLE DILIGENCE, TO ASCERTAIN THE RESIDENCE ADDRESSES OF THE FOLLOWING DEFENDANTS:

Check one: THIS ACTION SHOULD BE ASSIGNED TO: ☐ WHITE PLAINS ☑ MANHATTAN
(DO NOT check either box if this a PRISONER PETITION.)

DATE 06/01/2011 SIGNATURE OF ATTORNEY OF RECORD
Daniel DiNapoli Daniel P. DiNapoli

RECEIPT #

ADMITTED TO PRACTICE IN THIS DISTRICT
[ ] NO
[X] YES (DATE ADMITTED Mo. 04 Yr. 2010)
Attorney Bar Code #DD-4790

Magistrate Judge is to be designated by the Clerk of the Court.

Magistrate Judge _____ is so Designated.

Ruby J. Krajick, Clerk of Court by _____ Deputy Clerk, DATED _____.

UNITED STATES DISTRICT COURT (NEW YORK SOUTHERN)

Addendum Regarding Related Case Now Pending in S.D.N.Y.:

This case is related to *Pfizer Inc., et al v. Actavis Inc. et al*, 1:10-cv-08197-TPG (filed October 29, 2010), which is currently pending in the Southern District of New York. Both cases involve plaintiff Pfizer Inc. suing for infringement of its patent: U.S. Patent No, 6,469,012, (the "'012 patent") titled "Pyrazolopyrimidinones for the Treatment of Impotence." In both cases, the defendants are generic companies who have submitted Abbreviated New Drug Applications to the FDA seeking approval under the Federal Food, Drug and Cosmetic Act to market and sell, prior to the expiration of the '012 patent, 25 mg, 50 mg, and 100 mg tablets of sildenafil citrate, generic copies of Viagra®, for treatment of erectile dysfunction.